JACC Vol. 27, No. 6
May 1996:1444–9

Basal Release of Endothelium-Derived Nitric Oxide at Site of Spasm in Patients With Variant Angina

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Objectives. **The aim of this study was to investigate the basal release of nitric oxide at spastic sites in patients with variant angina.**

Background. **We previously reported that endothelium-dependent dilator responses to acetylcholine, substance P and bradykinin are preserved at the site of coronary artery spasm. However, it is not known whether the basal release of endothelium- derived nitric oxide is altered at the spastic site.**

Methods. **The effects of intracoronary N^G-monomethyl-L-arginine (L-NMMA, an inhibitor of nitric oxide synthesis) at cumulative doses of 50, 100 and 200 μmol on basal coronary artery tone were investigated in eight patients with variant angina and normal coronary angiograms and in eight control subjects. The lumen diameters of large epicardial coronary arteries were assessed by quantitative coronary arteriography.**

Results. **Coronary spasm was provoked by the intracoronary administration of acetylcholine in all patients with variant angina. L-NMMA did not alter the arterial pressure and heart rate but significantly decreased the coronary artery diameter at spastic and nonspastic sites. Constrictive responses to L-NMMA were significantly greater ($p < 0.01$) at the spastic site (constriction by 200 μmol, 22 ± 7%, mean ± SD) than at the nonspastic site (10 ± 7%). Constrictive responses to L-NMMA at the nonspastic site in patients with variant angina were comparable to those in the control subjects.**

Conclusions. **These findings support the hypothesis that the basal release of nitric oxide may not be decreased at the spastic site in patients with variant angina.**

(J Am Coll Cardiol 1996;27:1444–9)

The vascular endothelium plays an important role in the maintenance of vascular tone by releasing various dilating and constricting substances (1–3). Recently, an important endothelium-derived relaxing factor has been identified as nitric oxide or a related compound (4,5). L-Arginine analogues such as N^G-monomethyl-L-arginine (L-NMMA) inhibit the synthesis of nitric oxide at rest and under conditions of acetylcholine stimulation in animals and humans (3). Quyyumi et al. (6) have investigated the effects of the intracoronary infusion of L-NMMA in patients with normal coronary arteriograms and have suggested that nitric oxide contributes to the resting coronary artery tone in the human coronary circulation.

The pathogenesis of coronary artery spasm is related closely to the process of atherosclerosis (7,8). The angiographic location of coronary artery spasm has been linked to histologic evidence of intimal thickening in swine (9–11) and human (12) models of coronary spasm. Therefore, it is plausible that even in the absence of angiographically detectable atherosclerosis, there might be some degree of early atherosclerotic changes at the sites of coronary artery spasm. Although atherosclerosis may impair endothelium-dependent dilation to acetylcholine (1–3,13–15), endothelium-related vasodilator responses to substance P and calcitonin gene-related peptide are preserved at atherosclerotic segments in humans (16,17). We (18–20) have demonstrated that endothelium-dependent vasodilator responses to acetylcholine, substance P and bradykinin are preserved at the spastic site in patients with variant angina. However, it is unknown whether the basal production or release of nitric oxide is altered at the spastic site in such patients. Indeed, basal coronary artery tone is elevated at the spastic site in a subgroup of patients with variant angina (19,21–23). The latter finding may imply that the decreased production of some dilator substances, including nitric oxide, may contribute to the elevated basal tone. Therefore, we designed this study to investigate whether the basal release of nitric oxide is altered at the spastic site in patients with variant angina.

Methods

Study cohort. Eight patients with variant angina and normal coronary arteriograms (mean age 68 ± 8; four men, four women) were studied (Table 1). All patients with variant

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Manuscript received October 31, 1995; revised manuscript received December 31, 1995, accepted January 9, 1996.

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0735-1097/96/$15.00
PII S0735-1097(96)00021-6

Table 1. Patient Characteristics

Pt No.	Age (yr)/Gender	Cholesterol Level (mg/dl)	Smoking	HT	DM	Drugs Before the Study	Spastic Site*	Control Site*
1	67/F	206	−	+	−	N	seg6	seg11
							seg7	seg8
							seg14	seg12
2	60/F	207	−	−	−	D,N	seg6†	seg14
3	59/F	213	−	−	−	−	seg8†	seg14
4	46/M	159	+	−	−	−	seg11	seg7
							seg12	seg9
5	61/M	148	+	−	−	D	seg14	seg13
							seg7†	seg9
6	63/M	256	+	+	−	D,N	seg11†	seg13
7	54/M	188	+	+	−	−	seg6	seg11
8	73/F	234	+	+	−	D	seg8†	seg7

*Location of spasm site as defined by the American Heart Association. †Coronary blood flow was measured at the proximal segment (seg) of the spastic site before and after intracoronary N^G-monomethyl-L-arginine. D = diltiazem; DM = diabetes mellitus; F = female; HT = arterial hypertension; M = male; N = nitrate; Pt = patient; + = yes; − = no.

angina had a typical history of anginal pain at rest. In these patients, coronary artery spasm (lumen reduction ≥75%) associated with ischemic ST segment elevation (n = 5) or depression (n = 3) was angiographically provoked in one or more segments of the left coronary artery by the intracoronary infusion of acetylcholine (100 μg/min into the left coronary artery) as previously described (16,17). Five of eight patients complained of anginal chest pain during the provoked spasm. Patients in whom diffuse spasm was provoked or the spasm occurred in peripheral segments were excluded.

Eight patients with atypical chest pain and normal coronary arteriograms (mean age 57 ± 9; five men, three women) in whom neither coronary artery spasm, chest pain nor ischemic ST segment changes were provoked by acetylcholine were studied as control subjects. Patients with a history of myocardial infarction, valvular heart disease or left ventricular dysfunction were excluded.

Risk factors for coronary atherosclerosis examined in this study included hypercholesterolemia (total cholesterol >220 mg/dl), essential hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg), smoking, age >60 years, family history of ischemic heart disease and diabetes mellitus (fasting blood glucose ≥140 mg/dl or a positive glucose tolerance test). Of eight patients with variant angina, two were free of risk factors, one had one risk factor, three had two risk factors and two had four risk factors (Table 1). Of eight control subjects, three were free of risk factors, two had one risk factor, two had two risk factors and one had four risk factors. Thus, there was no significant difference in the risk factor profiles between the two groups.

Quantitative coronary arteriography. Coronary arteriograms were recorded and analyzed in a blinded manner using a Siemens angiographic system (Bicor and Hicor, Siemens-Asahi Inc.). An appropriate view that permitted clear visualization of the artery to be studied was selected. The angle of the view, the distance from the X-ray focus to the object and that from the object to the image intensifier were kept constant during the study. An end-diastolic arteriogram frame was selected, and the lumen diameter of the large epicardial coronary artery was determined using a validated densitometric analysis system as previously described (18,19). Readily identifiable branch points were determined as reference markers to allow assessment of serial changes in the diameter at the same arterial site. Changes in the diameter in response to drugs were expressed as percent changes from the baseline value.

In patients with variant angina, we determined changes in the lumen diameter at 12 paired spastic and nonspastic sites (Table 1). The nonspastic site was defined as an adjacent segment proximal or distal to the spastic site or as a segment of another, nonspastic vessel with a baseline diameter similar to that at the spastic site. In control subjects, we determined changes in the lumen diameter at segments of the left coronary artery with a baseline diameter similar to that at the spastic site in patients with variant angina.

Measurements of coronary blood flow velocity and blood flow. Changes in coronary blood flow in response to L-NMMA were measured in five patients with variant angina and eight control subjects. A 6F Judkins catheter was placed at the left main coronary artery via a femoral approach. A 0.018-inch (0.46 mm) Doppler-tipped, guide wire (FlowWire, Cardiometrics Inc.) was then advanced into the left coronary artery through the Judkins catheter. The tip was placed at the proximal segment of the spastic site in patients with variant angina and at the proximal segment of the left anterior descending or left circumflex coronary artery in the control subjects. Before and during the infusion of L-NMMA, the peak coronary blood flow velocity was monitored continuously using a fast Fourier transform-based spectral analyzer (FlowMap). Using arteriography, we determined changes in the lumen cross-sectional area at a segment 3 to 5 mm distal to the tip of the FlowWire. Systemic arterial pressure and heart rate were

Table 2. Effects of L-NMMA on Mean Arterial Pressure, Heart Rate, Coronary Artery Diameters and Coronary Blood Flow

		L-NMMA (cumulative dose, μmol)		
	Baseline	50	100	200
Patients with variant angina				
Mean arterial pressure (mm Hg)	86 ± 14	84 ± 11	85 ± 12	94 ± 11
Heart rate (beats/min)	71 ± 9	69 ± 9	69 ± 9	72 ± 9
Coronary artery diameter (mm)				
Control site	2.35 ± 0.59	2.38 ± 0.59	2.31 ± 0.63	2.10 ± 0.58*
Spastic site	2.25 ± 0.44	2.32 ± 0.45	2.20 ± 0.44	1.75 ± 0.36†
Coronary blood flow (ml/min)	42 ± 19	41 ± 18	40 ± 18	29 ± 14*
Control patients				
Mean arterial pressure (mm Hg)	83 ± 8	84 ± 9	88 ± 10	90 ± 9
Heart rate (beats/min)	66 ± 6	64 ± 9	67 ± 9	66 ± 9
Coronary artery diameter (mm)	2.32 ± 0.86	2.30 ± 0.88	2.29 ± 0.89	2.11 ± 0.74*
Coronary blood flow (ml/min)	44 ± 21	45 ± 20	37 ± 14	32 ± 13*

*$p < 0.05$. †$p < 0.01$ versus before N^G-monomethyl-L-arginine (L-NMMA) by one-way analysis of variance followed by Bonferroni multiple comparison test. Data are mean ± SD.

continuously recorded. The steady-state signals were used for analysis.

The mean peak blood flow velocity was determined, and the coronary blood flow (CBF) was calculated using the following formula:

$$\text{CBF (ml/min)} = 0.5 \times \text{mean peak CBF velocity (cm/min)} \times \text{cross-sectional area (cm}^2\text{)}.$$

Following the L-NMMA study, the FlowWire was withdrawn from the coronary artery and the Judkins catheter.

Study protocol. The study protocol was approved by the Institutional Review Committee on Human Research of the Research Institute of Angiocardiology, Kyushu University School of Medicine. Written informed consent was obtained from each patient.

Cardiac catheterization was performed in the fasting state after oral premedication with 5 mg of diazepam. Antianginal or antihypertensive medications were discontinued at least 24 h before the study (Table 1). After the baseline coronary arteriography had been completed, the following protocols were performed.

First, the effects of N^G-monomethyl-L-arginine (L-NMMA, CLINALFA Inc.) on coronary vasomotor responses were studied. After steady-state baseline hemodynamic parameters were recorded for 3 min and coronary arteriography was performed, L-NMMA at doses of 50, 50, and 100 μmol (cumulative doses of 50, 100, and 200 μmol) were infused over 1 min into the left coronary artery through the Judkins catheter. Two minutes after the beginning of each dose of L-NMMA, when hemodynamic parameters had stabilized, coronary arteriography was performed. We then waited for 1 min before administering the next dose of L-NMMA. We confirmed that these doses of L-NMMA completely inhibited acetylcholine (10 μg/min)-induced dilation of large epicardial coronary arteries and acetylcholine-induced increases in coronary blood flow in patients with atypical chest pain and normal coronary angiograms (24).

Second, acetylcholine was administered into the left coronary artery (100 μg/min), and then into the right coronary artery (50 μg/min), to provoke coronary artery spasm. Coronary arteriography was performed 2 min after injection of acetylcholine.

Third, coronary arteriograms in multiple projections were recorded to assess the severity of atherosclerotic lesions 2 min after isosorbide dinitrate was administered into the left and right coronary arteries. When angina or ischemic ST segment elevation occurred in patients with variant angina following the administration of acetylcholine, isosorbide dinitrate was immediately administered into the spastic coronary artery, and coronary angiograms were recorded. The basal coronary artery tone was defined as the percent dilation in response to isosorbide dinitrate.

Statistical analysis. Data are expressed as the mean ± SD in the text and the mean ± SE in figures. Analysis of variance (ANOVA) for repeated measures followed by the Bonferroni multiple comparison test was used to compare serial changes in hemodynamic parameters in response to graded doses of L-NMMA. A Student *t* test was used to compare responses to isosorbide dinitrate. A probability level <0.05 was considered statistically significant.

Results

Patient characteristics. Table 1 shows clinical characteristics such as age, gender and serum cholesterol concentration as well as a history of arterial hypertension, smoking or antianginal and antihypertensive drugs used before the study in patients with variant angina.

Effects of L-NMMA. Changes in the coronary artery diameter and other hemodynamic variables in response to intra-

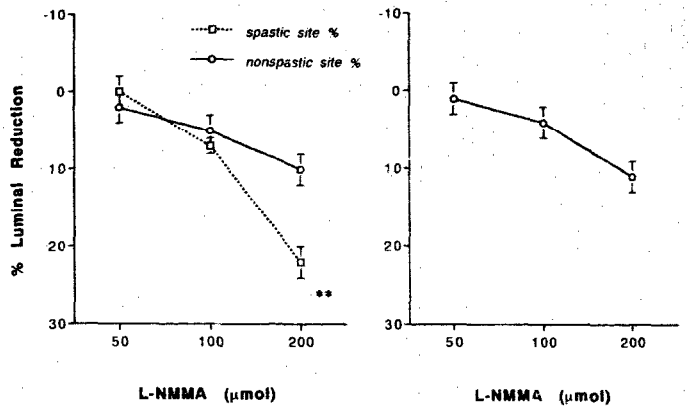

Figure 1. Line graphs of the effects of the intracoronary administration of L-NMMA on the percent changes in the diameter of epicardial arteries (lumen reduction) in patients with variant angina (**left**) and control subjects (**right**). Data are presented as the mean ± SE. L-NMMA = N^G-monomethyl-L-arginine. **$p < 0.01$ versus the control site by two-way analysis of variance followed by Bonferroni multiple comparison test.

coronary L-NMMA are shown in Table 2. In patients with variant angina, the baseline lumen diameters at the spastic site did not significantly differ from those at the nonspastic site. L-NMMA did not significantly alter arterial pressure and heart rate but significantly decreased the lumen diameters at both the spastic ($p < 0.01$) and nonspastic ($p < 0.05$) sites. There was no significant difference in the responses of the lumen diameters to L-NMMA between the two sites. However, the percent decrease in the lumen diameter evoked by L-NMMA was significantly greater ($p < 0.01$ by two-way ANOVA) at the spastic site than at the nonspastic site (Fig. 1).

There was no significant difference between patients with variant angina and control subjects concerning the baseline mean arterial pressure, heart rate, the lumen diameters of the large epicardial coronary arteries or their responses to L-NMMA (Table 2). The percent decrease in the lumen diameter in the control subjects did not differ significantly from that at the nonspastic site in patients with variant angina (Fig. 1).

L-NMMA significantly decreased coronary blood flow in five patients with variant angina and eight control subjects (Table 2). There was no significant difference between patients with variant angina and the control subjects concerning the baseline coronary blood flow and its response to L-NMMA.

Provocation of coronary artery spasm. The intracoronary administration of acetylcholine after L-NMMA provoked coronary artery spasm at one or more segments in all eight patients with variant angina involving a total of 12 sites (Table 1). The acetylcholine-induced spasm occurred at 12 sites in eight patients. The percent decrease in lumen diameter induced by acetylcholine at the spastic sites (88 ± 10%) was significantly greater ($p < 0.01$) than that at the nonspastic sites (36 ± 11%).

In control patients, intracoronary acetylcholine after L-NMMA caused neither anginal pain, coronary artery spasm, nor ischemic ST segment changes. The percent decrease in lumen diameter induced by acetylcholine was 31 ± 9% in these patients.

Effects of isosorbide dinitrate. The intracoronary administration of 2 mg isosorbide dinitrate did not change the mean arterial pressure or heart rate but significantly increased the diameter of the coronary artery. The percent increase in the diameter at the spastic site (27 ± 11%) was significantly greater ($p = 0.01$) than that at the nonspastic site (17 ± 7%) in patients with variant angina. However, the percent increase in the diameter at the nonspastic site in patients with variant angina did not differ from that in controls (16 ± 8%).

Coronary arteriography after isosorbide dinitrate revealed that all patients and control subjects had angiographically normal coronary arteries.

Discussion

We previously reported that endothelium-dependent vasodilating responses to acetylcholine, substance P and bradykinin are preserved at spastic sites in patients with variant angina and normal coronary arteriograms (18–20). However, the basal release of nitric oxide at such spastic sites has not been investigated. The novel finding in this study is that intracoronary L-NMMA caused greater constriction at spastic sites than nonspastic sites in patients with variant angina.

Nitric oxide and basal coronary artery tone. Nitric oxide is produced continuously by the endothelium in the absence of external stimulus in vivo. This is termed basal release. The shear stress caused by blood flow is the major stimulus for this phenomenon. L-Arginine analogues such as L-NMMA inhibit the release of nitric oxide from the endothelium at rest and under conditions of acetylcholine stimulation (1–6). The intracoronary infusion of L-NMMA causes coronary vasoconstriction in animals and humans in vivo (1,2,6). We have recently reported that intracoronary infusion of L-NMMA (total 200 μmol) completely abolished acetylcholine-induced dilation of large epicardial coronary arteries in patients with normal coronary arteriograms (24). In this study, the intracoronary

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infusion of L-NMMA (total 200 μmol) significantly decreased the basal lumen diameter of epicardial coronary arteries in patients with variant angina and control subjects. Thus, data from the present study and previous report (6) suggest that nitric oxide may contribute to the control of basal coronary artery tone at angiographically normal sites in humans.

Basal release of nitric oxide at site of spasm. We found in this study that the magnitude of constriction induced by the high dose (200 μmol) but not the low doses (50 and 100 μmol) of L-NMMA was greater at the spastic site than at the nonspastic site (Fig. 1). Quyyumi et al. (6) have demonstrated that L-NMMA-induced constriction of large epicardial coronary arteries in patients with normal coronary arteriograms is decreased by the presence of risk factors for coronary atherosclerosis. However, it is unlikely that these altered responses of the spastic site to L-NMMA in patients with variant angina were caused by the presence of risk factors, because both the spastic and nonspastic sites were exposed to identical risk factors in each patient. Because there was no significant difference in the risk factor profiles between patients with variant angina and controls, our finding that constricting responses to L-NMMA of the nonspastic sites in patients with variant angina did not differ significantly from those in control subjects is consistent with the findings of Quyyumi et al. (6). Because the decreases in coronary blood flow in response to L-NMMA were comparable between patients with variant angina and controls, it is unlikely that the altered responses to L-NMMA at the spastic site resulted from changes in the coronary blood flow in response to L-NMMA. L-NMMA did not significantly change the arterial pressure or heart rate. Therefore, it is likely that the coronary vasoconstriction induced by intracoronary L-NMMA resulted largely from the decreased release of nitric oxide from the endothelium.

Although the nitric oxide-generating capacity was not investigated directly in the present study, our finding of an altered vasoconstricting response to L-NMMA at the spastic site may suggest the following possibilities. First, the results of recent investigations have suggested that the expression of endothelial constitutive nitric oxide synthase mRNA and nitric oxide protein production are not impaired but rather are augmented in atherosclerotic blood vessels in animals (25–27) and humans (28). In addition, inducible nitric oxide synthase mRNA has been found in macrophages and vascular smooth muscle within human atherosclerotic vessels (28). Thus, our present data are in agreement with the suggestion that the nitric oxide-generating capacity might be increased at spastic sites. Second, it has been reported that the production of endothelium-derived constricting factors such as endothelin (1,2) and superoxide radicals (29) also is augmented in atherosclerotic vessels. Coronary spasm usually results from nonspecific local hyperreactivity to vasoconstricting stimuli that produce only mild constriction at nonspastic sites (7,8). Thus, it is possible that the blockade of nitric oxide synthesis by L-NMMA unmasked the effects of constrictor stimuli so that the vasoconstricting response to L-NMMA was apparent at the spastic site. In any case, our present observations suggest that the basal release of nitric oxide may not be decreased at spastic sites in patients with variant angina. It should be noted that coronary constriction in response to the intracoronary infusion of N^{ω}-nitro-L-arginine methyl ester at the spastic site did not differ from the response at the control site in our swine model of coronary spasm (11).

Previous studies also have shown that the basal tone (the percent dilation in response to isosorbide dinitrate) was augmented at spastic sites where coronary artery spasm was provoked by the intracoronary administration of acetylcholine or ergonovine in patients with variant angina (21–24). This also was observed in the present study. However, our present observations do not suggest that a decreased release of nitric oxide contributed to the increased basal tone at the spastic sites.

Limitations of the present study. The major limitation of this study is the fact that the spasm provocation test was performed after L-NMMA had been infused into the coronary artery. Thus, we must consider the possibility that the responses to acetylcholine might have been influenced by the presence of L-NMMA. However, all patients with variant angina and atypical chest pain underwent the same protocol, and coronary artery spasm was provoked by acetylcholine only in patients with variant angina. We previously have reported, in our swine model of coronary spasm, that the intracoronary infusion of N^{ω}-nitro-L-arginine methyl ester augmented the magnitude of serotonin-induced constriction at nonspastic sites but did not affect serotonin-induced spasm at spastic sites (11). These findings suggest that the inhibition of nitric oxide synthesis with L-arginine analogues may not influence the provocation of coronary artery spasm. Another limitation is that patients with normal coronary arteriograms were studied. Thus, we do not exclude the possibility that constrictor responses to L-NMMA at spastic sites might be altered in patients with advanced coronary atherosclerosis.

Conclusions. Our present observations suggest that the basal release of nitric oxide may not be decreased at spastic sites in patients with variant angina and normal coronary arteriograms.

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